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MINIMISING ANTIBIOTIC RESISTANCE TO *STAPHYLOCOCCUS AUREUS* IN DEVELOPING COUNTRIES
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ABSTRACT

Objective: **To assess the role of rational drug use and laboratory services in preventing the emergence of multiple antibiotic resistant *Staphylococcus aureus* in developing countries**
Data source: **Literature search on compact disk-read only memory (CD-ROM) Medline and Internet using the key words: *Staphylococcus* and antibiotic resistance. A few articles were manually reviewed.**
Study selection: **Relevant studies or articles on antibiotic resistance with special reference to Eastern Africa, region are included in the review.**
Data extraction: **From individual studies or articles.**
Data synthesis: **Evidence for the spread of *S. aureus* multiple antibiotic resistance is synchronized under the headings: Introduction, current situation, antibiotic resistance control strategies, are outlined.**
Conclusion: **There is need for concerted efforts between different groups to monitor changes in the epidemiology and antibiotic resistance of *S. aureus*. Strategies aimed at preventing transmission of resistant strains are remarkably effective when strictly enforced. Necessary attention should be given on the subject so that meaningful control measures preventing the expansion of antimicrobial resistance can be formulated, thereby ensuring the future successful treatment of Staphylococcal infections.**

INTRODUCTION

Staphylococcal infections continue to pose important clinical problems. *S. aureus* is one of the major causes of community-acquired and hospital-acquired infections(2-4)· Its main habitats are the nasal membranes and skin of warm blooded animals, in which it causes a wide range of infections from mild, such as skin infections and food poisoning, to life threatening, such as pneumonia, sepsis, osteomyelitis and infectious endocarditis(5). Several antibiotics have been used in combination as empiric antimicrobial therapy for some of these infections, especially aminoglycosides, penicillins, cephalosporins and vancomycin as a consequence of the constantly changing antimicrobial susceptibility patterns(6-8). Antibiotic resistance among the Staphylococci has rendered therapy of these infections a therapeutic challenge. Although antibiotic resistance is a worldwide problem, developing countries face special difficulties because alternative and effective therapeutic options are either unavailable or unaffordable(9). Effective action to prevent the spread of resistance will not only ameliorate a major problem but also demonstrate that different groups can work together on difficult issues.

The discovery of penicillin in 1929 by Fleming, and its therapeutic efficacy heralded the development of many successful antimicrobial agents(10,11). Most of the antimicrobial agents were discovered as actinomycete products by the late 1950s. In addition to the screening efforts, chemical modifications of penicillins, cephalosporins and aminoglycosides began in 1960s resulting in the synthesis of many useful derivatives. The decade of the 1980s was marked by acceleration in the development of new antimicrobial compounds. The early part of 1980s was dominated by introduction of multiple new beta-lactams, extended spectrum penicillins and third generation cephalosporins while the later part saw the introduction of carbapenem(12).

ANTIMICROBIAL RESISTANT *S. AUREUS*: THE CURRENT SITUATION

There has been much interest in the media, national and international in the potential for the development of "super bugs", by which is usually meant pathogenic bacteria resistant to all available antibiotics. We have witnessed a recent burst of methicillin or multiple resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *S. aureus* (VRSA) and other bacteria in patients and the environment(2,3,8,13).

This shows that the battle against bacteria is never ending. Accurate determination of the magnitude of MRSA requires detection of mecA gene, which encodes for resistance to methicillin. Drugs of choice in patients due to MRSA are glycopeptide agents such as vancomycin and teichoplanin(14). Vancomycin was the only antibiotic effective against it, but, in 1997, vancomycin resistant *S. aureus* was also isolated(15). Vancomycin resistant *S. aureus* is the pathogen of greatest concern.

Another compounding factor is the treatment of *S. aureus* is the frequency of resistance to both the older and newer, third generation cephalosporins and other commonly used antibiotics(3,13). The resistance of *S. aureus* to antibiotics has led to the use of multiple drugs on a routine basis as a consequence of the constantly changing antimicrobial susceptibility pattern that are characteristic of the targeted bacteria. A major drawback is the newly recommended drugs are not readily available in the most developing countries, and if available are more expensive than those previously used(9,16-18).

Antimicrobial susceptibility testing should include antibiotics from several groups and having different modes of action. Resistant isolates should further be studied for their genetic mechanisms of resistance by means of molecular characterization. Bacteria posses a remarkable number of ways to become resistant to antibiotics, which can either be acquired or innate(19-21). These include genetic mutation which alter binding sites, production of enzymes that destroy or inactivate antimicrobials, changing to other metabolic systems not affected by antimicrobials and finally, altering the permeability of their cell membrane making it difficult for the antimicrobial to enter. Despite early uniform susceptibility to penicillin, *Staphylococcus* acquired penicillin-binding protein (PBP 2a), encoded by mecA gene elaborating penicillinase that rendered penicillin inactive and that is borne by nearly all the clinical isolates(22). Methicillin resistance may also be associated with mechanisms independent of mecA gene such as hyper production of beta lactamase or methicillinases. Most methicillin resistant *Staphylococci* are multi-resistant, and the mec region may harbour several resistance determinants resulting in a clustering of resistance genes within this region(22). Penicillinase-resistant beta-lactams such as methicillin were introduced in 1960s but resistance to these has become an increasing concern(2,3,13,22). In some developed countries, upto 60% of all hospital-acquired infections are due to resistant bacteria and majority are caused by *S. aureus*(23). Vancomycin, which is recommended in MRSA, is usually not available in most developing countries.

STRATEGIES TO MINIMISE AND CONTROL ANTIBIOTIC RESISTANCE IN *S. AUREUS*

Laboratory Services: Laboratory services are an essential component of' curative and preventive health care activities worldwide. Laboratory investigations are a vital part of the clinical assessment and the results determine selection of drugs for patient management. In addition to confirmatory diagnosis, laboratory records can be used for disease and drug surveillance.

The importance of surveillance of the antimicrobial susceptibility pattern cannot be over emphasized as a guide to the use of antimicrobial agents. Surveillance will assist to define the extent of resistance among different pathogens and in different populations, to adjust treatment strategies and national drug policies and to measure the success of intervention strategies. In East African countries, laboratory services have been established as part of the national health structure from the central hospital through each level of health care delivery to health centers and even dispensary level. Primary Health Care (PHC) is first level of contact of individuals with the health care system, and is accessible to the majority of the rural population in developing countries. In support of the primary health care strategies, World Health Organization Laboratory Technology programme adopted two major resolutions for the African region; to develop appropriate technology for health laboratories, and encourage member states to develop health laboratory services(24). With currently available facilities and manpower, health centers are usually the smallest health units offering laboratory services. Since they are usually situated in more peripheral areas and are more numerous, health centers provide the first line comprehensive diagnostic, curative and preventive medical services for the majority of the population. Unfortunately, these laboratories are far from offering antibiotic sensitivity testing services. Frequently, antibiotics (included in drug kit) are prescribed and administered to patients without laboratory diagnosis and determination of antibiotic sensitivity patterns. Worse still, the administration of antibiotics is often given to patients with viral or fungal infections. Broad-spectrum antibiotics are frequently given in place of specific ones to substitute for bacterial identification and sensitivity testing. Intensive use of antimicrobial agents for prophylaxis and treatment of patients in hospitals make them a prime site for emergence, maintenance and spread of resistant pathogens(25). This may lead to drug wastage and emergence of more resistant bacterial strains(26). Prevention of emergence of antibiotic resistance during treatment is therefore an important goal when prescribing antimicrobials.

Problems affecting the operation of laboratories at the peripheral level are widespread. These include lack of properly designed laboratory rooms, unreliable access to clean water or electrical power, shortage of equipment and supplies, lack of effective equipment maintenance services and little regular support supervision from higher units(27). Consequently, the laboratories are functioning below capacity. There is need for laboratory

networking to the central or National Public Health Reference Laboratory to support less developed/equipped peripheral units that cannot even do culture and sensitivity for surveillance activities. At the 7th Annual Scientific Conference of the Kenya Association of Clinical Pathologists in 1999, it was suggested that there was need to improve laboratory services in health facilities and reinforce strict regulations governing both private and government laboratories.

In the East African countries, supplies for laboratory services are put in the budget together with drugs and medical supplies. Health authorities give priority to treatment drugs when operating under severe economic constraints. Furthermore, the impact of laboratory services in improving diagnosis and rationalizing drug use is not widely appreciated by medical personnel or patients. National and international authorities should be encouraged to channel more resources into the development of PHC laboratory services. However, the long-term benefits of improved diagnosis are not known, and the issues of cost reduction and whether early diagnosis at outpatient level can reduce hospital admissions are being addressed. Due to the increasing prevalence of antimicrobial resistant *S. aureus* strains, surveillance and effective treatment remain an important tool for the management of infections caused by this agent. Improved disease recognition improves the accuracy of reporting and contributes to effective national health planning(28). Co-operation and support between countries on a regional and international basis, together with patient education and demand for quality services, are necessary to ensure widespread access to essential laboratory services at primary health care level in Africa.

National surveillance and monitoring programmes: Although many factors may be able to influence whether bacteria become insensitive to an antibiotic, the two main forces are prevalence of resistance genes and the extent of antibiotic use(20). There is no simple cure for resistance, but opportunities for control lie in the lesser and better use of antibiotics backed by swifter and more accurate diagnosis and susceptibility testing, developing new antibiotics and in protecting old ones from developing resistance. All this must be supported by good local knowledge of the epidemiology of inflections and the likelihood of particular antibiotic pressure to select resistance. The laboratory may serve as a key surveillance point of information gathering and dissemination for antimicrobial resistance data. For instance, in the Netherlands (1989-1995), about 0.3% of *S. aureus* isolates were resistant to methicillin and non to vancomycin(29), while in Kenya, the prevalence of methicillin resistant *S. aureus was* 39.8% but addition of clavulonic acid to amoxycillin increased the susceptibility three-fold(13). The low prevalence may be due to restrictive use of antibiotics and to strict isolation measures aimed at eradicating methicillin resistant *S. aureus.* Methicillin resistance was particularly associated with consumption of broadspectrum beta-lactams, quinolones and total antibiotic consumption in the ward. Thus antibiotic policy is an important factor for limiting the emergence and spread of multiresistant bacteria within the hospital environment(30). Currently, most hospitals in developing countries do not have any antibiotic policy. Hospitals should have a programme for online antibiotic surveillance of drugs used in various units in order to change the empiric treatment when there is an increase in antibiotic resistance. It is also important to carry out a survey of antibiotic consumption in order to avoid further selective pressure on bacteria showing increased resistance rates. To prevent and control nosocomial infections, there is need to increase national surveillance for infection rates so that inter hospital comparisons are valid and work with health care workers on better implementation of existing control measures such as hand washing and physical barrier nursing techniques. Critical factors that influence any laboratory on monitoring antimicrobial resistance include availability of high quality discs to measure antibiotic sensitivity and participating in an active quality control and proficiency testing programme to ensure the validity of the results generated. Such a network is not yet in place.

Nosocomial infections caused by *S. aureus* are as a result of cross infection between patients and hospital staff and tend to spread rapidly(8). Protective measures for patients as well as staff must be applied and maintained. The level of protection is high if disposable products are used. Thus disposable materials to decrease the incidence of nosocomial infections should replace re-usables. In addition, hospital infection control committees need to be set up and taken more seriously. At Nairobi Hospital in Kenya, the problem of MRSA was recognised in midyear of 1996 among both in and out patients. Swift action by the hospital infection control committee resulted in no more cases at the end of the year(2). The national referral hospital (Kenyatta National Hospital) also has a functional infection control committee. These may serve as role models to disseminate information to smaller hospitals. As a step forward, the Infection Control Association of Kenya (ICAK) was launched in 1997 to coordinate infection control countrywide and provide an effective communication and networking channel between various target and interested groups.

There is increasing concern regarding the efficacy of many disinfectants on the market. MRSA was found to be significantly less susceptible than methicilin sensitive *S. aureus* (MSSA) to chlorhexidine digluconate, 'Hibiscrub' and 'Hibisol'. Hand disinfectants containing both alcohol and chlohexidine ("Hibisol") are more effective against MRSA than scrubs based only on chlorhexidine (Hibiscrub') and should be used in clinical practice(31). It is therefore important to select appropriate concentration of disinfectant and rationally use them

for disinfection and hospital hygiene. There is a possibility that a significant proportion of laboratory or hospital acquired infections may partly be due to the use of ineffective or low concentration of disinfectants. A continuous monitoring of the afficacy of the commonly used disinfectants is necessary in order to minimise the risk of infection by antibiotic resistant microorganisms, which are common in the hospital.

Rational drug use policy development and implementation: Programmes to improve rational and effective drug use in developing countries are urgently needed. In industrialised nations, most antibiotics are available only on prescription, but this restriction does not ensure proper use. Patients often fail to use the full course of treatment, then stock pile the left over doses and medicate themselves, or their family and friends in less doses than therapeutic amounts. In these circumstances, the improper dosing will fail to eliminate the disease agent completely and exert a strong selective pressure on the development of both chromosome and plasmid mediated resistance, by destroying susceptible bacteria in a population permitting resistant ones to proliferate. This is a major factor limiting long-term successful use of an antimicrobial agent, with infections that were once easy to treat now proving quite difficult(21). Unfortunately, when resistance becomes a clinical problem, those countries that often do not have access to expensive drugs may have no substitute available.

In developing countries, antibiotic use is even less controlled such that many antibiotics are available off the counter(32,33). A study of antibiotic sale behavior in retail chemist shops in Nairobi revealed that about 64% of chemists sell antibiotics without doctors prescriptions, and most shops sold under dose drugs according to the request of the patient(32). Surveys need to be undertaken to determine the risk of dispensing errors, factors contributing to the occurrence of dispensing errors, the number of prescription items that one pharmacist can safely dispense in a day. whether countries should have a regulatory maximum dispensing load and all estimation of the number of recent errors at the pharmacist's work place. In Australia the principle contributing factors were high prescription volumes, pharmacists' fatigue, over work, interruptions to dispensing and similar or confusing drug names(34). In addition one of the factors necessary to improve the risk of dispensing errors is to improve the doctors handwritings. Dispensing errors are occurring in numbers well above reports to regulatory authorities and seem to be accepted as part of the practice. If drugs are to retain their efficacy over pathogens, they have to be used more responsibly. Standards need to be set appropriately.

Antibacterial substances are used in considerable amounts as growth promoters in animal husbandry and for therapeutic purposes. There are however incalculable risks for human health resulting from the use of particular feed additives(35). The application of molecular methods to typing, and characterisation of bacteria and their resistance genes has provided more concise evidence for the transfer of antibiotic resistance to glycopeptides and streptogramins among animals and humans. In Kenya, a high frequency of antibiotic resistance among *S.aureus* isolates from milk and meat could be attributed to their use in treatment of disease in animal husbandry(36). Contact with these animals or consumption of flood products from them has been the main route of dissemination of resistance to the human population. This demonstrates how resistant bacteria arising from indiscriminate use of antibiotics in animals may impact on human health.

Problems of cost sharing in government health facilities are enormous. Utilization of outpatient services in government owned district hospitals in Dar-es-Salaam declined by more than 50% following the introduction of user charges in these health facilities in mid July 1993(37). In such circumstances, patients may resort to self-medication with consumption of inadequate doses of antibiotics which result in low levels of antibiotics in the blood stream, a condition conducive to the selection of resistance mutant(32). This may be partly due to economic constraints coupled with ongoing structural adjustments programmes faced by the patients. Employees medical covers are almost a thing of the past. Worse still the money levied on patients is not necessarily used at the point of service. For instance, some countries have highlighted the need to allow the laboratory service to retain most of the funds from charges levied on laboratory tests as one of the ways to sustain health laboratory services(28). Clear policy guidelines on the rational use of antibiotics need to be drawn up and reinforced(9).

Education (formal and informal)

Infection control Association of Kenya (ICAK) has been vigorously promoting educational programmes in the field of infection prevention and control for practitioners and health units countrywide in the form of workshops. Among key areas addressed are establishing infection control units in hospitals, emergence of drugs resistance and the role of antiseptics/ disinfectants in infection control.

In many developing countries people seek treatment in pharmacy(38). Pharmacists usually fail to recognise the infection and provide treatment most often with ineffective regimens. Educational interventions and improved couselling of patients for prevention is needed to improve disease recognition, treatment and referral practises. In Vietnam, the main reason for not taking full course of antibiotics are not economic constraints, but purchases' poor knowledge about antibiotics(33). The study documents the need for better health education about rational use of antibiotics in the general public. In Kenya, most shops sold under-dose drugs according

to the request of the patient(32). Training shopkeppers as a channel for information to the community is both feasible and likely to have a big impact on behaviour changes in malaria control and probably other infectious diseases(39), including those that may be due to *S. aureus.*

CONCLUSION

The epidemiology and antibiotic sensitivity of *S. aureus* is changing worldwide. Although it is important to search for newer and more effective antibiotics, it is imperative that we develop a surgical mindset of appropriate antibiotic stewardship(40). Tackling antibiotics resistance require combined effort by the health care providers and the patients at large. The use of single dose prophylactic regimen, using narrow spectrum agents when possible for therapeutic indications, limiting the duration of therapeutic agents appropriately, avoiding the use of vancomycin except when necessary and the adhering to strict infection control measures are all steps that will limit the spread and development of resistance organisms. The existence of a large reservoir genes in healthy individuals and the environment in developing countries represents a threat to the success of antimicrobial therapy. Antibiotic resistance in developing countries needs to be monitored closely. If drugs are to retain their efficacy over pathogens, they must be used more responsibly especially for those in developing countries where health budgets are meager and the cost of newer drugs ever increasing. Empirical treatment of infections in the absence of susceptibility data is widely practised in health facilities. It is important that collaborative national and international studies on the incidence of antibiotic resistance are performed on a repetitive basis. Thus there is need for laboratory networking to cover the whole country and international collaboration support to health services. Results of such surveillance network will allow for more economical and efficacious drugs prescribing, and selection of essential drug list.

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REFERENCES

1. Rice, L.B. Successful interventions for resistance to extended spectrum beta antibiotics. *Pharmacotherapy*. 1999; **19:**120-137.
2. Hayanga, A., Okello, A. Husein, R. and Nyong'o, A. Experience with methicillin resistant *Staphylococcus aureus* at the Nairobi hospital. *East Afr. Med. J.* 1997; **74:**203-204.
3. Urassa, W.K., Haule, E.A., Kagoma, C. and Langeland, N. Antimicrobial susceptibility of *Staphylococcus aureus* strains at Muhimbili Center, Tanzania. *East Afr. Med. J.* 1999; **76:**693-695.
4. Malonza, I.M., Omari, M.A., Bwayo, J.J. *et al*. Community acquired bacterial infections and their antimicrobial suspeceptibility in Nairobi, Kenya. *East Afri. Med. J.* 1997; **74:**166-170
5. Kotisso, B., and Aseffa, A. Surgical wound infection in a teaching hospital in Ethiopia. *East. Afri. Med. J.* 1998; **75:**402-405.
6. Gakuu, L.N. Review of methicillin resistant *Staphyloccocus aureus* with special reference to handling surgical patients *East Afr. Med. J.* 1997; **74:**198-202.
7. Weinstein, R.A. Nosocomial infection update. *Emerging infect. Dis.* 1998; **4:**416-420.
8. Ayliffe, G. Methicillin-resistance *Staphylococcus aureus* (MRSA) update. *Postgrad. Doctor*. 1999; **21:**16-20.
9 Kariuki, S. Kenya antibiotic resistance. *Lancet.* 1997; **349:**(S111):9.
10. Fleming, A. On the antibacterial action of culture of a penicillium, with special reference to their use in the isolation of *B influenzae. Brit. J. Exp. Pathol.* 1929; **10:**226-236.
11. Chain, E., Floney, H.W., Gardner, A.D., *et al*. Penicillin as a chemotherapeutic agent. *Lancet*. 1940; **11:**226-228.
12. Sutcliffe, J. and Nafsika, H. Emerging targets in antimicrobial resistance and antifungal chemotherapy, 1st edition. Geogopapadokou. Chapman and Hall, 1991.
13. Omari, M.A., Malonza, I.M., Bwayo, J.J., *et al.* Pattern of bacterial infections and antimicrobial susceptibility at Kenyatta National Hospital Nairobi, Kenya. *East Afr. Med. J.* 1997; **74:**134-137.
14. Patterson, D.L. Reduced susceptibility of *Staphylococcus aureus* to vancomycin–a review of current knowledge. *Comm. Dis. Intell*. 1999; **18:**69-73.
15. Hiramatsu, K. Arikata, N. and Hanaki, H. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet*. 1997; **350:**1668-1671.
16. Dornbusch, K., King, A. and Legakis, N. Incidence of antibiotic resistance in blood and urine isolate from hospitalised patients. Reports from a European collaborative study. European study group A on antibiotic resistance (ESGAR). *Scand, J. Infect. Dis.* 1998; **30:**281-288.
17. Obi, C.L., Makandiramba, B,. Tswana, S.A., *et al. In vitro* disc diffusion of sensitivity meropenem against bacterial pathogens in Harare. *East Afr. Med. J.* 1999; **76:**365-369
18. Hart, C.A. and Kariuki, S. Antimicrobial resistance in developing countries. (Review). *Brit. Med. J.* 1998; **317:** 647-650.
19. McManus, M.C. Mechanisms of bacterial resistance to antimicrobial agents. *Hlth Sys. Pharm.* 1997; **54:**1420-1433
20. Levy, B.S. The challenge of antibiotic resistance. *Scientific American*. 1998; **398:**1-10.
21. Levy, B.S. The Confronting multidrug resistance: a role for each of us (community). *J. Amer. Med. Ass.* 1993; **269:**1840-1842.
22. Brakstad, G.O. and Maeland, J.A. Mechanisms of methicillin resistance *Staphylococcus aureus Acta Path Micro. Imm. Scand.* 1997; **104:**204-270.
23. Kariuki, S.M. and Hart, C.A. Epidemiological aspects of methicilin drug resistance. *East Afr. Med. J.* 1997; **74:**124-128.
24. WHO Resolution. Strategies for improving the quality of care in health care institution in the African region. 1995 AFR/C45/R3.
25. AI Harbi, M. Antimicrobial prophylactic practice in surgical patients, *East Afr. Med. J.* 1998; **75:**703-707.
26. Waiyaki, P.G. Bacterial drug resistance, diarrhoeal diseases and laboratory diagnosis of pulmonary tuberculosis (editorial). *East Afr. Med. J.* 1993; **70:**259-262.

27. Kassu, A. and Aseffa, A. Laboratory services in health centers within Amhara region, North Ethiopia. *East Afr. Med. J.* 1999; **76:**239-242.
28. Carter, J.Y. Editorial. Role of laboratory services in health care. The present status in Eastern Africa and recommendations for the future. *East Afr. Med. J.* 1999; **76:**237-238.
29. De Neeling, A.J., van Leeuwen, W.J., Schouls, L.M., *et. al*. Resistance of *Staphylococcus* in Netherlands: Surveillance by an electronic network during 1989-1995. *J. Antimicrob. Chemother.* 1998; **41:**93-101.
30. Monsen, T., Ronmark, M., Olofsson, C. and Winstrom, J. Antibiotic susceptibility of *Staphylococcus aureus* isolated in blood cultures in relation to antibiotic consumption in hospital wards. *Scand. J. Infect, Dis.* 1999; **31:**399-404.
31. Krampf, G., Jarach, R. and Ruden, H. Limited effectiveness of chlorhexidine based hand disinfectants against methicillin resistant *Staphylococcus aureus* (MRSA). *J. Hosp. Infect.* 1998; **38:**297-303.
32. Indalo, A.A. Antibiotic sale behavior in Nairobi: a contributing factor to antimicrobial drug resistance. *East Afr. Med. J.* 1997; **74:**171-173.
33. Van Duong, D., Binns, C., W. and Van le, T. Availability of antibiotics as off-the-counter drugs in pharmarcies: A threat to public health in Vietnam. *Trop. Med. Inter. Hlth*. 1997; **2:**1133-1139.
34. Peterson, G.M., Wu, M.S. and Bergin, J.K. Pharmacist's attitudes towards dispensing errors: their causes and prevention. *J. Clin. Pharmacy and Therapeutics*. 1999; **24:**57-71.
35. Witte, W., Klare, I. and Werner, G. Selective pressure by antibiotics as feed additives. *Infection*. 1999; **27:**35-38.
36 Ombui, J.N., Kimotho, A.M. and Nduhiu, J.G. Antimicrobial resistance patterns and plasmid profiles of *Staphylococcus aureus* isolated from milk and meat. *East Afri. Med. J.* 2000; **77:**463-467.
37. Hussein, A.K. and Musinda, P.G.M. Impact of user charges on government health facilities in Tanzania. *East Afr. Med. J.* 1997; **74:**749-750.
38. Garcia, P.J., Gotuzo, E., Hughes, P. and Holmes, K.K. Syndromic management of STDs in pharmacies: evaluation and randomised intervention trial. *Sex Trans. Dis.* 1998; **74:**153-158.
39. Marsh, V.M., Mutemi, W.M., Muturi, J., G. *et al* Changing home treatment of childhood fevers by training shop keepers in rural Kenya. *Trop. Med. Inter. Hlth.* 1999; **4:**383-389.
40. Postier, R.G. Antibiotic-resistance organism infection. *Amer. Surg.* 2000; **66:**112-116.